Betrixaban

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Publication date:
2018

Betrixaban: Impact on routine and specific coagulation assays - Practical laboratory guidance

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ECTH 2018
European Congress on Thrombosis and Haemostasis
Marseille, France
24 - 26 October

Introduction and aim

Betrixaban is a novel oral direct factor Xa inhibitor approved by the Food and Drug Administration for prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute illness at risk for thromboembolic complications. As for other DOACs, assessment of the anticoagulant effect of betrixaban may be useful in some situations. Also, clinicians need to know how routine coagulation assays are influenced.

The aim of this study is to determine which coagulation assay(s) should be used to assess the impact of betrixaban on hemostasis and provide laboratory guidance for their interpretation.

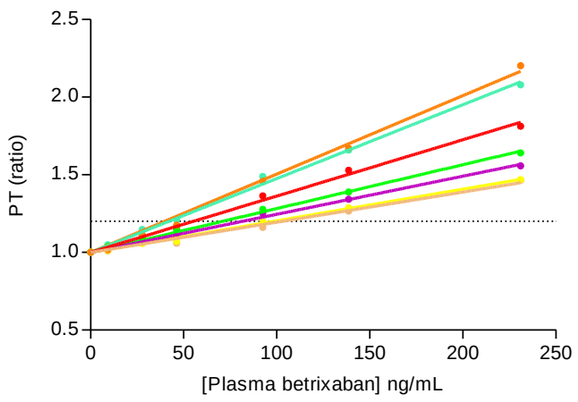
Methods

Betrixaban was spiked at final concentrations ranging from 0 to 250 ng/mL in platelet-poor plasma. These concentrations cover the on-therapy range (from ± 9 ng/mL at C_{trough} to ± 122 ng/mL at C_{max} for 40 and 120 mg once daily dose, respectively). We tested the impact of betrixaban on prothrombin time (PT), activated partial thromboplastin time (aPTT), dilute Russel viper venom time (dRVVT), chromogenic anti-Xa assays, thrombin generation assay (TGA) and a large panel of hemostasis diagnostic tests using different reagents from several manufacturers.

Results : Betrixaban influence routine and specific coagulation assays

A concentration-dependent prolongation of aPTT, PT and dRVVT is observed. The sensitivity mainly depends on the reagent. FXa chromogenic assays show high sensitivity and a linear correlation both depending on the reagent and/or the methodology. Several methodologies applicable for other direct factor Xa inhibitors have to be adapted. As for others direct FXa inhibitors, chromogenic anti-Xa assays are the most sensitive assays for the measurement of betrixaban in a routine setting. However, only two methodologies appear to be adapted to the low levels of betrixaban observed in pharmacokinetic studies. For others chromogenic assays, procedures need to be adapted to increase the sensitivity. Some parameters of the TGA (especially peak and mVRI) are very sensitive to the presence of betrixaban but the lack of standardization and its turnaround time reduce its implementation in routine.

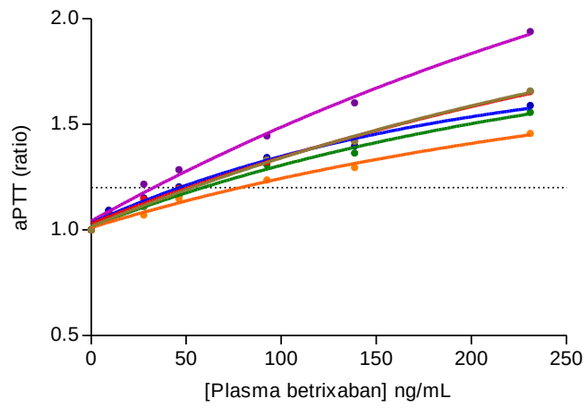
Impact of betrixaban on PT



- STA®-Neoplastine® R (r^2= 0.99; 2xCT= 198 ng/mL; CV= 0.6%)
- TriniCLOT® PT HTF (r^2= 0.99; 2xCT= 491 ng/mL; CV= 0.9%)
- TriniCLOT® PT Excel (r^2= 0.99; 2xCT= 354 ng/mL; CV= 1%)
- TriniCLOT® PT Excel S (r^2= 0.99; 2xCT= 210 ng/mL; CV= 0.5%)
- RecombiPlasTin 2G® (r^2= 0.99; 2xCT= 407 ng/mL; CV= 1.1%)
- STA®-Neoplastine® CI+ (r^2= 0.99; 2xCT= 276 ng/mL; CV= 0.7%)
- Dade® Innovin® (r^2= 0.99; 2xCT= 514 ng/mL; CV= 1%)

Betrixaban showed a concentration dependent prolongation of the prothrombin time. The relation was linear and the 2xCT depended on the reagent. The 2xCT was ranging from 198ng/mL for STA-Neoplastine R® to 514ng/mL for Dade® Innovin®.

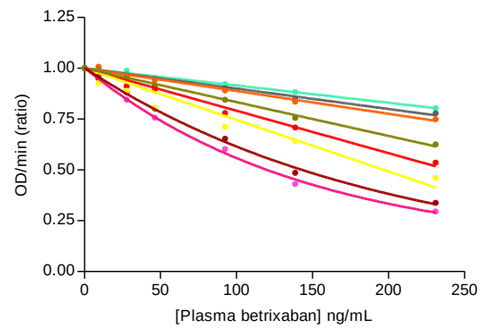
Impact of betrixaban on aPTT



- SynthAfax® (r^2= 0.99; 2xCT= 257ng/mL; CV= 0.9%)
- STA®-PTT Automate (r^2= 0.99; 2xCT= NC; CV= 0.6%)
- STA®-Cephascreen® (r^2= 0.99; 2xCT= NC; CV= 0.4%)
- SynthASil® (r^2= 1.00; 2xCT= NC; CV= 1.2%)
- STA®-C.K. Prest® (r^2= 0.99; 2xCT= 479ng/mL; CV= 1%)
- Actin® FS (r^2= 0.99; 2xCT= 474 ng/mL; CV= 0.9%)

Betrixaban showed a concentration dependent prolongation of the aPTT. The relation was curvilinear and the 2xCT depended on the reagent. The 2xCT was ranging from 257 ng/mL for SynthAfax® to 479 ng/mL for C.K. Prest®.

Measurement of betrixaban pharmacodynamics with chromogenic anti-Xa assays

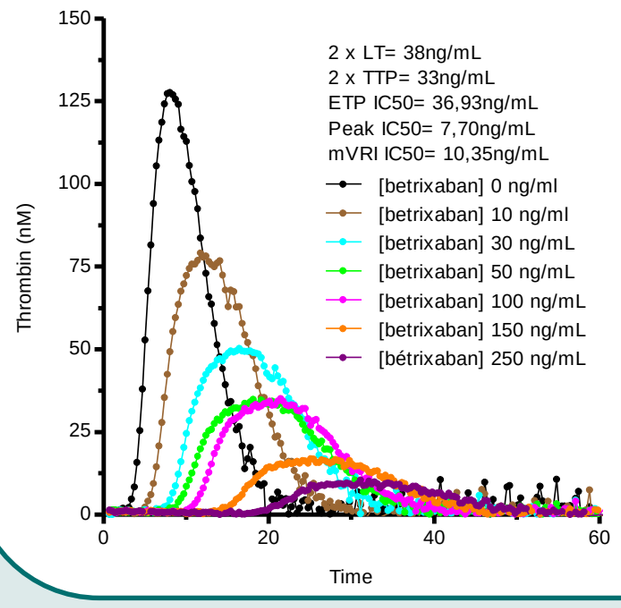


- Technochrom® Anti-Xa High (r^2= 0.96; ½xOD/min= 569 ng/mL; CV= 1.3%)
- Technochrom® Anti-Xa (r^2= 0.99; ½xOD/min= 240 ng/mL; CV= 0.9%)
- HemosIL® Liquid Heparin (r^2= 0.97; ½xOD/min= 197 ng/mL; CV= 3.1%)
- Biophen® Heparin LRT® (r^2= 0.99; ½xOD/min= 499 ng/mL; CV= 0.6%)
- Biophen® Direct Factor Xa Inhibitors® (r^2= 0.98; ½xOD/min= 447 ng/mL; CV= 0.8%)
- STA®-Liquid Anti-Xa (r^2= 0.99; ½xOD/min= 300 ng/mL; CV= 0.7%)
- Biophen® Heparin LRT® Low (r^2= 1.00; ½xOD/min= 120 ng/mL; CV= 1.5%)
- Biophen® Direct Factor Xa Inhibitors® Low (r^2= 0.99; ½xOD/min= 143 ng/mL; CV= 1.5%)

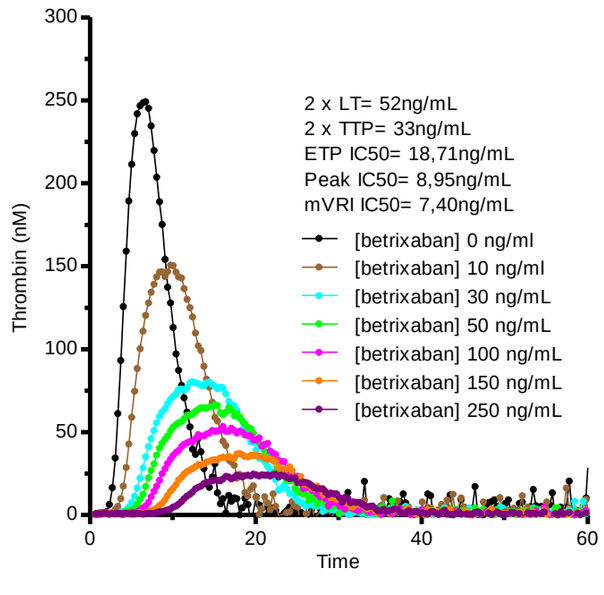
There was a concentration-dependent decrease of the OD/min. Tests with higher baseline OD/min had a wider range of quantitation compared to those starting at lower OD/min at baseline.

Impact of betrixaban on calibrated automated thrombogram®

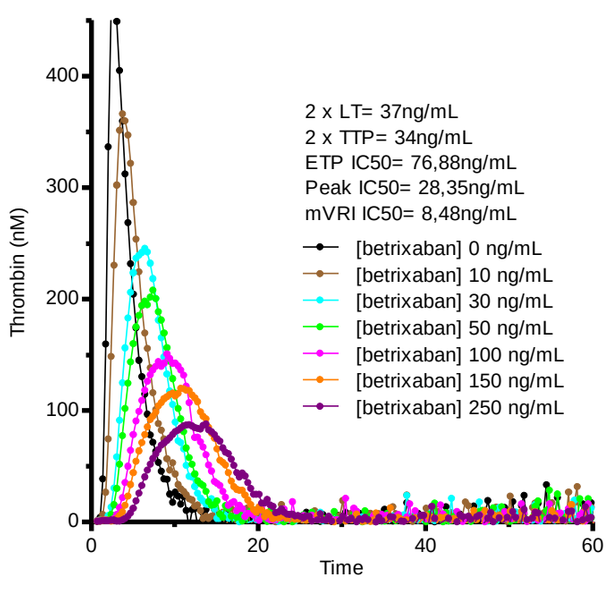
PPP-Reagent LOW



PPP-Reagent



PPP-Reagent High



The most influenced CAT® parameters are the peak and the mean velocity rate index. There is an inter-reagent variability. Thanks to their low IC_{50} for the peak and the mVRI, the better resolution and their large range of application, PPP-Reagent and PPP-Reagent High seemed to be the best reagents to monitor patients on betrixaban. (ETP: Endogenous Thrombin Potential; IC_{50}: half-maximum inhibitory concentration; LT: Lag Time; mVRI: mean Velocity Rate Index; TTP: Time to Peak). mVRI was defined as follow: (Peak) / (Time to Peak – Lag Time).

Betrixaban also affect diagnostic tests : for factors of the intrinsic pathway (FVIII, FIX, FXI and FXII), the aPTT-based clotting method showed a mean decrease of ± 5% at 10 ng/mL of betrixaban, 26% at 50 ng/mL and 58% at 150 ng/mL. The impact was more pronounced for FXI and FVIII. For FV, FVII and FX, a mean decrease of 1% at 10 ng/mL of betrixaban, 9% at 50 ng/mL and 25% at 150 ng/mL was observed, while prothrombin measurement seemed to be less affected (maximal decrease of 6% at 150 ng/mL) (*Data not shown*).

Conclusion

Adapted-chromogenic anti-Xa assays are the most appropriate assays to measure the pharmacodynamics of betrixaban in a routine setting. Betrixaban significantly affects several hemostasis diagnostic tests and this must be taken into consideration when requesting and interpreting such tests.

Contact

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